REMARKS

Reconsideration and withdrawal of the rejection of all the claims now in the application (i.e. Claims 1, 9, 11-13, 17-19, 22-27, 29 and 30 pending in the application) is respectfully requested in view of the foregoing amendments and the following remarks. Claims 3-6, 8 and 28 have been cancelled herewith.

Initially, the Examiner rejected claims 21, 25, 26, and 28-30 as being anticipated by Pratt et al. U.S. Patent No. 4,849,223. The Examiner considered that this reference disclosed an implant having metallic silver combined with titanium oxide or tantalum oxide and implants containing any microbial coatings comprising silver ions. The Examiner indicated that the surface of the device could be smooth, however the Examiner did not indicate that the reference taught polishing the surface as understood in the orthopedic implant art.

The Examiner also rejected claims 25-27 as being anticipated by Jacobson et al. U.S. Patent No. 5,180,585. The Examiner considered that this reference taught an antimicrobial coating comprising silver ions in polyetherekeytone (PEEK) and polylactic acid.

Applicant has amended the claims to include the requirement that the coating have magnesium and silver or copper ions mixed into the coating material. None of the references cited by the Examiner teach magnesium mixed into the matrix forming the coating. Column 7, lines 49 onward of the '585 reference teach that an optional hydrous metal oxide outer layer can be applied. There is no teaching that such can mixed into the matrix of the layer containing the antimicrobial ions.

The Examiner then rejected claims 1, 3-6, 8, 9, 11-15, 17-19, 21-23, and 25-30 as being obvious over a combination of Davidson U.S. Patent No. 5,685,306, Pratt et al., and Jacobson et al. With regard to claim 17, the Examiner considered that one of the embodiments of the '306 patent is that of a pacemaker lead, electrical signal transmitter or defibrillator. The Examiner considered that an external source would apply the electrical voltage in the defibrillator and signal transmitter embodiments and that the voltage would be applied to the surface of the device, electrostatically charging the surface of the devices. The Examiner provided no incentive to combine that teaching with the use of an antimicrobial coating over the device which coating would hinder the electrostatic charging of the surfaces as suggested by the Examiner. Thus, it is the position of the Applicant that the use of electrical voltages in the defibrillator and signal transmitter embodiments teaches away from applying a plastic coating over the implant. Even if such a coating were applied, as admitted by the Examiner in paragraph

3 of his Office Action, there is no teaching that such a coating could include ions having an antibacterial effect.

Regarding the polishing of the metal surface, the Examiner considers that the polishing step is used to sterilize the surface which is incorrect. Once polished, an implantable device has to be sterilized in a standard manner prior to packaging. A discussion of standard sterilization techniques is contained in the attached article by Anne Simmons in Medical Device Manufacturing and Technology 2004 which discusses the four methods used to sterilize medical devices such as steam, EtO sterilization, radiation sterilization, and gas plasma sterilization. Thus, one skilled in the art would understand that polishing is not used to sterilize the device but, in the context of the present invention, used to provide a surface which limits the adhesion of bacteria to the implant surface. Polishing of implants is discussed in U.S. Patent Nos. 5,171,275, 5,593,452, and 6,748,834. The purpose of polishing of devices in these patents is to reduce friction and wear and to allow for subsidence of the implant within bone cement.

As discussed above, Applicant has amended the claims to include the limitation that anti-microbial the layer contains a mixture of magnesium and silver or copper ions. That such a mixture can be used is discussed in paragraphs 22 and 23 of the application in which the substance that releases the ions is applied in a matrix or can be mixed into the implant material directly. Such a mixture containing magnesium (see paragraph 9 of the specification) is not disclosed in the prior art cited by the Examiner. Consequently, Applicant believes that none of the prior art either alone or in combination teaches a medical device coated with an anti-microbial material containing magnesium. Nor does it disclose a polished or charged surface with such a coating.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: January 26, 2005

Respectfully submitted,

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Sterilisation of Medical Devices

a report by
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Medical devices are sterilised to eliminate living organisms including bacteria, yeasts, mould and viruses.[1] Many sterilisation techniques are available today and these include the traditional methods of autoclaving, ethylene oxide (EtO) and gamma irradiation and the more recently introduced systems involving low-temperature gas plasma and vapour phase sterilants. Despite the availability of a wide range of sterilisation techniques, it is generally agreed that no single sterilisation process is capable of sterilising all medical devices without adverse effects. All processes have their own inherent advantages and disadvantages and many adverse effects relate to incompatibilities between polymers used in biomedical applications and sterilisation process parameters.

Sterilisation processes act on micro-organisms in a chemical or physical way. Generally, each process results in a lethal change in the structure or function of the organic macromolecules in the micro-organism, leading to death or the inability to reproduce. The macromolecules of biomedical polymers can be attacked by the same mechanisms, and different forms of sterilisation may result in hydrolysis, oxidation, softening, melting, chain scission and depolymerisation. Research has shown that sterilisation can modify the bulk and surface properties and alter the physiochemical stability of biomedical polymers.[2-5] Sterilisation may also result in the formation of degradation products, which may present a toxicological risk.[6]

When selecting a sterilisation method, an analysis of the compatibility of each device, particularly the chemical composition of the materials, with the process parameters of the sterilisation method and the chemicals used, is necessary. This article briefly describes the most widely used methods of sterilisation for medical devices and some of their effects on biomedical polymers.

Steam Sterilisation

Steam sterilisation or autoclaving is a relatively simple process that exposes the device to saturated steam at 121°C for a minimum of 20 minutes at a pressure of 121kPa.[7] The process is usually carried out in a pressure vessel designed to withstand the elevated temperature and pressure and kills micro-organisms by destroying metabolic and structural components essential to their replication. It is the method of choice for sterilisation of heat-resistant surgical equipment and intravenous fluid as it is an efficient, reliable, rapid, relatively simple process that does not result in toxic residues.

The high temperature, humidity and pressure used during the steam sterilisation process can lead to hydrolysis, softening or degradation of many biomedical polymers.[1] Several workers[8,9] have reported that autoclaving is unsuitable for the sterilisation of many biomedical polymers due to unacceptable changes in mechanical properties and surface degradation. A further issue is the potential formation of degradation products[6] during autoclave sterilisation of these materials.

Anne Simmons is an Associate Professor in the Graduate School of Biomedical Engineering at the University of New South Wales, Sydney, Australia. Her areas of research include the mechanical properties of biological and synthetic polymers, development of mechanical testing regimes for these materials, the effect of sterilisation on novel biomaterials, development of *in vivo* animal models for the determination of host and material responses and evaluation of functional, blood-contacting materials and devices. Before joining the university in mid 1999, she worked in the medical device industry for more than 17 years in the areas of research and development, clinical and regulatory affairs, strategic planning and senior management. Professor Simmons has extensive experience in managing collaborative research with universities, industry and other research organisations as well as broad knowledge of the development, manufacture and commercialisation of biomedical technology internationally.

1. *Anderson J M, Bevacqua B, Cranin A N, Graham L M, Hoffman A S, Klein M, Kowalski J B, Morrissey R F, Obstbaum S A, Ratner B D, Schoen F J, Sirakian A and Whittlesey D (1996),* Implants and Devices, in Biomaterials Science *(Eds Ratner B D, Hoffman A S, Schoen F J and Lemons J E), Academic Press: London. pp. 415–420.*
2. *Lerouge S, Guignot C, Tabrizian M, Ferrier D, Yagoubi N and Yahia L, "Plasma-based sterilization: effect on surface and bulk properties and hydrolytic stability of reprocessed polyurethane electrophysiology catheters",* J. Biomed. Mater. Res., *52(4) (2000), pp. 774–82.*
3. *Nair P D, "Currently practised sterilization methods—some inadvertent consequences",* J. Biomater. Appl., *10(2) (1995), pp. 121–35.*
4. *Mazzu A L and Smith C P, "Determination of extractable methylene dianiline in thermoplastic polyurethanes by HPLC",* J. Biomed. Mater. Res., *18(8) (1984), pp. 961–8.*
5. *Shintani H and Nakamura A, "Analysis of a carcinogen, 4,4'-methylenedianiline, from thermosetting polyurethane during sterilization",* J. Anal. Toxicol., *13(6) (1989), pp. 354–7.*
6. *Lelah M D and Cooper S L (1986),* Polyurethanes in Medicine, *Boca Raton, Florida: CRC Press.*
7. *Booth A F (1999),* Sterilization of medical devices, *Buffalo Grove, Illinois: Interpharm Press.*

EtO Sterilisation

EtO sterilisation is used routinely to sterilise materials that cannot withstand the high temperatures of autoclaving. The EtO sterilisation procedure involves drawing a vacuum in the sterilisation vessel, after which EtO is injected at a concentration of 600–1,200mg/litre. The steriliser is maintained at the desired conditions of 30–50°C and 40% to 90% humidity for the duration of sterilisation, usually between two to eight hours. The critical parameters of the cycle are temperature, pressure, humidity, EtO concentration and gas dwell time. Following the sterilisation cycle, the chamber is then evacuated several times to remove residual EtO. Further aeration is usually required after removal from the chamber, with aeration time ranging from two hours to two weeks, depending on the device and packaging.[1]

EtO is the most widely used industrial sterilant for medical devices today. Its primary advantages are the low processing temperature and the wide range of compatible materials. Its bactericidal, sporicidal and viricidal effects result from alkylation of sulfhydryl, amino, carboxyl, phenolic and hydroxyl groups in nucleic acids, causing cell injury or death. The main disadvantage of EtO relates to the toxicity and suspected carcinogenicity of the gas and residuals in the product and manufacturing environment. A long aeration process is also required to remove EtO and its by-products from sterilised materials and this can affect inventory requirements.

Although alkylating reactions have been reported in some polymers when EtO interacts with chemical groups such as urethane and urea groups,[10] EtO exposure has little effect on the molecular weight, polydispersity, mechanical properties, surface composition or degradation rate of most biomedical polymers.[11–13] Several workers[2,9,10] have reported that EtO is unsuitable for the sterilisation of some biomedical polymers due to changes in molecular weight and mechanical properties and the appearance of surface degradation. Potential formation of degradation products is also an issue with EtO sterilisation.[14]

Radiation Sterilisation

Radiation sterilisation utilises ionising radiation to sterilise medical devices. Either gamma rays from a cobalt-60 (60Co) isotope source or machine-generated accelerated electrons can be used. Gamma irradiation is the most popular form of radiation sterilisation and is used when materials are sensitive to the high temperature of autoclaving but compatible with ionising radiation. Exposure is achieved when the materials to .be sterilised are moved around an exposed 60Co source for a defined period of time. The most commonly validated dose used to sterilise medical devices is 25kGy.[7]

The bactericidal effect of gamma irradiation is dependent on oxidation of biological tissue. It is a simple, rapid and efficacious method of sterilisation. However, high capital costs are a major disadvantage. Sterilisation of biomedical polymers using gamma irradiation is also known to result in physical changes in some biomaterials, including embrittlement, discolouration,[15–17] odour generation, stiffening,[18,19] softening, an increase or decrease in melt temperature[20] and decreases in molecular weight.[11,13,18]

The two mechanisms involved in these changes are chain scission and cross-linking. As a result of chain scission, low-molecular-weight fragments and unsaturated bonds may appear and gas may be evolved. Mechanical properties including tensile strength, elastic modulus, impact strength, shear

8. *Terheyden H, Lee U, Ludwig K, Kreusch T and Hedderich J, "Sterilization of elastic ligatures for intraoperative mandibulomaxillary immobilization"*, Br. J. Oral Maxillofac. Surg., *38(4) (2000), pp. 299–304.*
9. *Zhang Y Z, Bjursten L M, Freij-Larsson C, Kober M and Wesslen B, "Tissue response to commercial silicone and polyurethane elastomers after different sterilization procedures"*, Biomaterials, *17(23) (1996), pp. 2,265–72.*
10. *Abraham G A, Frontini P M and Cuadrado T R, "Physical and mechanical behavior of sterilized biomedical segmented polyurethanes"*, Journal of Applied Polymer Science, *65(6) (1997), pp. 1,193–1,203.*
11. *Hooper K A, Cox J D and Kohn J, "Comparison of the effect of ethylene oxide and gamma-irradiation on selected tyrosine-derived polycarbonates and poly(L-lactic acid)"*, Journal of Applied Polymer Science, *63(11) (1997), pp. 1,499–1,510.*
12. *Ries M D, Weaver K, Rose R M, Gunther J, Sauer W and Beals N, "Fatigue strength of polyethylene after sterilization by gamma irradiation or ethylene oxide"*, Clinical Orthopaedics and Related Research, *(333) (1996), pp. 87–95.*
13. *Goldman M, Gronsky R and Pruitt L, "The influence of sterilization technique and ageing on the structure and morphology of medical-grade ultrahigh molecular weight polyethylene"*, Journal of Materials Science – Materials in Medicine, *9(4) (1998), pp. 207–212.*
14. *Hirata N, Matsumoto K I, Inishita T, Takenaka Y, Suma Y and Shintani H, "Gamma-Ray Irradiation, Autoclave and Ethylene-Oxide Sterilization to Thermosetting Polyurethane – Sterilization to Polyurethane"*, Radiation Physics and Chemistry, *46(3) (1995), pp. 377–381.*
15. *Sturdevant M, "Plastics in Medicine: How Sterilisation Changes Long-Term Resin Properties"*, Plastics Engineering, *47(1) (1991), pp. 27–32.*

strength and elongation may be affected. Decreases in fatigue strength in some biomedical polymers have also been reported following gamma irradiation.[19] Embrittlement may occur and crystallinity may also change as chain scission continues.[21] Cross-linking generally results in an initial increase in tensile strength in polymers while impact strength decreases. The polymer becomes more brittle with increased dose. Polymers containing aromatic groups generally are much more resistant to radiation-induced degradation than are aliphatic polymers.[20] It is also well established that polymers containing methylene groups can experience cross-linking.

Gamma irradiation has also been reported to magnify surface defects in some biomedical polymers[10,21] and Fourier transform infrared (FTIR) studies[12,19,22] have indicated significant oxidation of the surface of some biomedical polymers.

Gamma irradiation also has undesirable consequences due to the potential production of toxic degradation products such as 4,4'-methylenedianiline (MDA) that can be produced when a high-molecular-weight polyurethane material decomposes as a consequence of irradiation.[6,14,23] Another study[24] investigating the cytotoxicity of polyurethane materials following various forms of sterilisation reports the phenomenon of complete cell lysis after contact with gamma-irradiated polyurethane samples believed to result from the effect of a low-molecular-weight by-product.

Gas Plasma Sterilisation

Plasma-based sterilisation is a promising alternative for low-temperature sterilisation of biomedical devices. Cold plasma is a partially ionised gas comprising ions, electrons, ultraviolet photons and reactive neutrals such as radicals, excited and ground-state molecules. It is created by the application of an electric or magnetic field to a solution such as hydrogen peroxide (H_2O_2).

Two commercial gas plasma sterilisation systems currently available are Sterrad™ and Plazlyte™. These systems use H_2O_2 and H_2O_2/peracetic acid (PAA) respectively as the sterilising agent. The Sterrad™ procedure comprises a 45-minute period during which vapourised H_2O_2 is diffused through the treatment chamber, following which 300 watts of radio-frequency power are applied at a pressure of 0.5 Torr to create the plasma. The plasma is maintained for a period sufficient to ensure complete sterilisation with a standard phase lasting 15 minutes. The total procedure takes approximately one hour.[25] Plazlyte™ uses PAA and H_2O_2 vapour treatment, which is alternated with downstream plasma treatment by microwave excitation of the low-pressure gas mixture comprising oxygen, hydrogen and argon. The equipment operates by vapourising the chemical agents and diffusing the vapour into the chamber, alternating with the plasma. At the end of sterilisation, the reactive species combine to form water and oxygen, eliminating the need for aeration.[8]

H_2O_2 works by the production of destructive hydroxyl free radicals, which can attack membrane lipids, DNA and other essential cell components.[26] Inactivation of micro-organisms is dependent on time, temperature and concentration. PAA is an oxidising agent that denatures protein, disrupts cell

16. *Hermanson N J and Steffen J F (1993), "The physical and visual property changes in thermoplastic resins after exposure to high energy sterilisation – gamma versus electron beam"*, Antec 93 Conference Proceedings.
17. *Hermanson N J, Navarette L and Crittendon P (1997), "The Effects of High-Energy and EtO Sterilisation on Thermoplastics"*, Medical Device and Diagnostic Industry Magazine.
18. *Deng M and Shalaby S W, "Effects of Gamma-Irradiation, Gas Environments, and Postirradiation Aging on Ultrahigh Molecular-Weight Polyethylene"*, Journal of Applied Polymer Science, *58(11) (1995), pp. 2,111–2,119.*
19. *Goldman M and Pruitt L, "Comparison of the effects of gamma radiation and low temperature hydrogen peroxide gas plasma sterilization on the molecular structure, fatigue resistance, and wear behavior of UHMWPE"*, J. Biomed. Mater. Res., *40(3) (1998), pp. 378–84.*
20. *Hemmerich K J (2000), "Polymer Materials Selection for Radiation-Sterilized Products"*, Medical Device and Diagnostic Industry Magazine.
21. *Goldman M, Lee M, Gronsky R and Pruitt L, "Oxidation of ultrahigh molecular weight polyethylene characterized by Fourier Transform Infrared Spectrometry"*, Journal of Biomedical Materials Research, *37(1) (1997), pp. 43–50.*
22. *Fisher J, Reeves E A, Isaac G H, Saum K A and Sanford W A, "Comparison of the wear of aged and non-aged ultrahigh molecular weight polyethylene sterilized by gamma irradiation and by gas plasma"*, Journal of Materials Science-Materials in Medicine, *8(6) (1997), pp. 375–378.*
23. *Shintani H and Nakamura A, "Formation of 4,4'-methylenedianiline in polyurethane potting materials by either gamma-ray or autoclave sterilization"*, J. Biomed. Mater. Res., *25(10) (1991), pp. 1,275–86.*
24. *Belanger M C, Marois Y, Roy R, Mehri Y, Wagner E, Zhang Z, King M W, Yang M, Hahn C and Guidoin R, "Selection of a polyurethane membrane for the manufacture of ventricles for a totally implantable artificial heart: blood compatibility and biocompatibility studies"*, Artif. Organs, *24(11) (2000) pp. 879–88.*
25. *Bathina M N, Mickelsen S, Brooks C, Jaramillo J, Hepton T and Kusumoto F M, "Safety and efficacy of hydrogen peroxide plasma sterilization for repeated use of electrophysiology catheters"*, J. Am. Coll. Cardiol., *32(5) (1998), pp. 1,384–8.*

wall permeability and oxidises sulphur bonds in proteins, enzymes and other metabolites.[26]

Gas plasma sterilisation is reported to be suitable for the sterilisation of metals, natural rubber, silicone and various polymers such as polyvinyl chloride, polyethylene and polyurethane.[8,10] However, it is not suitable with liquids, oils, powders, biological tissues, paper, cotton and linen. It has inferior penetrating ability compared with EtO, but both PAA and H_2O_2 perform more effectively than EtO in terms of biological kill and sterilant removal.[7] Other advantages of plasma sterilisation are that it is a fast, low-temperature process with no requirement for aeration.

Gas plasma sterilisation processes use strongly oxidative chemical sterilising agents, H_2O_2 and PAA and it is well known that these agents can induce surface oxidation of some biomedical elastomers.[2,19,27–30] However, no significant changes in molecular weight or mechanical or thermal properties have been reported in a range of studies.[2,19,22,25,29,30] Lerouge, et al.,[2,29] found that MDA was not detected following gas plasma sterilisation of polyurethanes.

Conclusion

A range of sterilisation procedures is available for medical devices. However, each method is known to adversely affect the mechanical and physical properties of some biomedical polymers. A detailed analysis of the sterilisation process and the materials used in the medical device will enable the selection of the most appropriate process for routine sterilisation. ■

26. *Rutala W A and Weber D J, "Disinfection of endoscopes: review of new chemical sterilants used for high-level disinfection"*, Infect. Control Hosp. Epidemiol., *20(1) (1999), pp. 69–76.*
27. *Meijs G F, McCarthy S J, Rizzardo E, Chen Y C, Chatelier R C, Brandwood A and Schindhelm K, "Degradation of medical-grade polyurethane elastomers: the effect of hydrogen peroxide in vitro"*, J. Biomed. Mater. Res., *27(3) (1993), pp. 345–56.*
28. *Baldry M G C, "The bactericidal, fungicidal and sporicidal properties of hydrogen peroxide and peracetic acid"*, J. Appl. Bacteriol., *54 (1983), pp. 417–423.*
29. *Lerouge S, Tabrizian M, Wertheimer M R, Marchand R and Yahia L, "Safety of plasma-based sterilization: surface modifications of polymeric medical devices induced by Sterrad and Plazlyte processes"*, Biomed. Mater. Eng., *12(1) (2002), pp. 3–13.*
30. *Gorna K and Gogolewski S, "Molecular stability, mechanical properties, surface characteristics and sterility of biodegradable polyurethanes treated with low-temperature plasma"*, Polymer Degradation and Stability, *79(3) (2003), pp. 475–485.*